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Gender and Survival: A Population-Based Study of 201,114 Men and Women Following a First Acute Myocardial Infarction

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OBJECTIVES We tested the hypotheses that the effect of gender on short-term case fatality following a first admission for acute myocardial infarction (AMI) varies with age, and that this effect is offset by differences in the proportion of men and women who survive to reach hospital.

BACKGROUND Evidence is conflicting regarding the effect of gender on prognosis after AMI.

METHODS All 201,114 first AMIs between 1986 and 1995 were studied. Both 30-day and 1-year case fatality were analyzed for the 117,749 patients hospitalized and for *all* first AMIs, including deaths before hospitalization. The effect of gender and its interaction with age on survival was examined using multivariate modeling.

RESULTS Gender-based differences in survival varied according to age in hospitalized patients, with younger women having higher 30-day case fatality than men (e.g., <55 years, women 6.5% vs. 4.8% men, $p < 0.0001$). When deaths from first AMI before hospitalization were included in 30-day case fatality, women were less likely to die (adjusted odds ratio 0.9, confidence interval 0.89 to 0.93). Gender was not an independent predictor of one-year survival ($p = 0.16$).

CONCLUSIONS Female gender increases the probability of surviving to reach hospital, and this outweighs the excess risk of death occurring in younger women following hospitalization. Overall, men have a higher 30-day case fatality than women. Women do not fare worse than men after AMI when age and other factors are taken into account. However, men are more likely to die before hospitalization. (J Am Coll Cardiol 2001;38:729–35) © 2001 by the American College of Cardiology

Although coronary heart disease (CHD) is perceived to be of greater importance in men, it is also the leading cause of death among middle-aged women in developed countries (1). Despite significant declines in coronary event rates worldwide (2,3) and advances in treatment (4), case-fatality rates following acute myocardial infarction (AMI) in both men and women remain high. Although it is generally considered that women have a worse prognosis than men following an AMI (5,6), the reasons for this are unclear, and there is conflicting evidence regarding the independent effect of gender on prognosis (7). In one of the largest recent studies examining this issue, Vaccarino et al. (8) demonstrated that of 384,878 patients surviving to reach hospital with an AMI, younger women, but not older women, had higher in-hospital case-fatality rates than men of the same age, and that the effect of gender could not be simply described. There is some evidence, at least in younger age groups, that such a difference in immediate case fatality could result from a greater number of women with a worse prognosis (or men with a better prognosis) surviving to admission, but having a higher in-patient case fatality thereafter (9).

The current study was designed to address the residual issues concerning gender-based differences in AMI-related case fatality. First, is there a gender-based difference in immediate case fatality in the entire population, including all age groups and including deaths in patients admitted to the hospital and those dying before admission? Second, if there are gender-based differences, do they persist in the longer-term, after discharge from hospital?

METHODS

Data source. A Scottish-wide retrospective study was carried out using the Linked Scottish Morbidity Record Database. Data on all National Health Service hospital admissions in Scotland are collected and collated by the Information and Statistics Division of the National Health Service (10). This database is linked to the Registrar General's death certificate data, with an accuracy of 98% (10). It contains information on deaths occurring both in and out of hospital. The Information and Statistics Division, Scotland, has a Scottish Morbidity Record Standards

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Abbreviations and Acronyms

AMI	= acute myocardial infarction
CHD	= coronary heart disease
CI	= confidence interval
OR	= odds ratio

Unit that checks a 1% sample of Scottish Morbidity Record One forms and compares the information with that recorded in the clinical case notes. In 1994 the accuracy of AMI as a principal diagnosis was 97% (11). As reported previously, we identified all patients admitted to Scottish hospitals between 1986 and 1995 with a diagnosis of first AMI ICD9 code 410 (12). We also identified all those individuals with a death certificate diagnosis of AMI who had not survived to reach hospital. Only the patient's first AMI was analyzed. A "first" AMI was defined as no prior hospital admission for AMI within at least five years of the index admission or death. The data were patient based and not episode based, so that no patients were counted twice in the analyses.

Baseline data. Each patient's record provided information on age, gender, postcode sector, date of admission, previous admissions and date of death if it occurred. Postcodes of residence were used to assign a Carstairs deprivation category ranging from one (least deprived) to five (most deprived) to each individual. These categories are derived from 1991 census data on the proportion of residents who are unemployed, live in overcrowded accommodations, do not have a car or belong to a low occupational social class (13). All prior hospital admissions within five years were also identified using retrospective linkage. There was a minimum of one-year follow-up for all patients.

Statistical analyses. We compared baseline data relating to men and women using chi-square tests for categorical data and *t* tests for continuous data.

INDIVIDUALS ADMITTED TO THE HOSPITAL. Case-fatality rates at 30 days and 1 year were compared in men and women who were categorized into five age groups. The age categories chosen were consistent with previous studies (14,15). Survival time was calculated as the time from hospital admission with a first AMI to death from any cause or to December 31, 1996. For those patients who were admitted to hospital, age and gender-specific case-fatality rates were calculated for 30-day follow-up using the actuarial life table method. Multiple logistic regression was used to calculate the adjusted odds ratio (OR) for the probability of death within 30 days of a first admission for an AMI. The first model included gender as an explanatory variable. Subsequent models included age, socioeconomic deprivation, comorbidity (as measured by prior hospital admission) and finally the interaction between age and gender. Logistic regression models were used to derive the adjusted relative risk of death at one year after excluding those patients who died within 30 days. Again, the first model included gender as an explanatory variable; age, socioeconomic deprivation, comorbidity, and the interaction between age and gender were added to subsequent models. As no significant departure from linear trend was found, age and its interaction with gender were modeled as continuous variables. Age was recoded into five categories to look at the independent effect of gender on survival within age groups. For each variable entered into a model, the lowest class was set at unity. Adequacy of fit was assessed using the Hosmer-Lemeshow Goodness-of-Fit-Test, and all tests of statistical significance were two-tailed.

ALL FIRST AMIs INCLUDING INDIVIDUALS WHO DID NOT SURVIVE TO REACH HOSPITAL. We identified all individuals between 1986 and 1995 whose death was principally attributed to a first AMI but who had not survived to reach hospital. These AMIs, in addition to all hospital admissions for first AMI, were considered to comprise all known first AMIs. The proportion of all first AMIs admitted to hospital was calculated for age and gender-specific categories. Age and gender-specific 30-day case-fatality rates were then applied to these proportions to derive a 30-day case-fatality rate that included those deaths from AMI that did not survive to reach hospital as well as deaths occurring subsequent to hospital admission. Kaplan-Meier survival curves were constructed for men and women from the survival data for all AMIs, and they were compared using the log-rank and Breslow tests.

Multiple logistic regression was used to calculate the adjusted OR for the probability of death before reaching hospital and also of surviving to 30 days following a first AMI. The first model included gender as an explanatory variable. Subsequent models included age, socioeconomic deprivation, comorbidity and finally the interaction between age and gender.

Significance was accepted at the 0.05 level. All analyses were undertaken using the Statistical Package for Social Scientists (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics. Table 1 shows the baseline characteristics of all 201,114 individuals with a known first AMI between 1986 and 1995 in Scotland (total population approximately 5.1 million) (16). Of this total, 117,749 (58.5%) survived to be admitted to hospital.

INDIVIDUALS ADMITTED TO HOSPITAL. On average, women were seven years older than men. The age distribution of men and women was thus significantly different, with twice the proportion of men under age 65 compared to women (49 vs. 25%, $p < 0.0001$). The proportion of men and women in each deprivation category was constant and reflected the overall gender distribution of the admission cohort. Overall, there were more individuals from the most deprived than from the least deprived category. Approximately 20% of the patients had been admitted to hospital in

Table 1. Baseline Characteristics of 201,114 Patients With a Known First AMI Between 1986 and 1995

	Admissions to Hospital (n = 117,749)		Did Not Survive to Reach Hospital (n = 83,365)		All First AMIs (n = 201,114)	
	Men	Women	Men	Women	Men	Women
Total, 1986–1995	68,626	49,123	44,655	38,710	113,281	87,833
Mean age yrs (SD)	64.3 (12)	71.6 (11)	71.1 (11)	77.7 (10)	67.0 (12)	74.3 (11)
Age group						
< 55 years	14,702 (21.4%)	3,855 (7.8%)	3,788 (8.5%)	931 (2.4%)	18,490 (16.3%)	4,786 (5.4%)
55–64 years	18,923 (27.6%)	8,668 (17.6%)	8,177 (18.3%)	3,419 (8.8%)	27,100 (23.9%)	12,087 (13.8%)
65–74 years	22,069 (32.2%)	16,704 (34.0%)	15,228 (34.1%)	9,640 (24.9%)	37,297 (32.9%)	26,344 (30.0%)
75–84 years	11,150 (16.2%)	15,113 (30.8%)	13,652 (30.6%)	15,150 (39.1%)	24,802 (21.9%)	30,263 (34.5%)
>84 years	1,782 (2.6%)	4,783 (9.7%)	3,810 (8.5%)	9,570 (24.7%)	5,592 (4.9%)	14,353 (16.3%)
Deprivation categories						
I—least deprived	11,105 (16.2%)	7,701 (15.7%)	7,110 (15.9%)	6,662 (17.2%)	18,215 (16.1%)	14,363 (16.4%)
II	12,823 (18.7%)	9,017 (18.4%)	9,118 (20.4%)	7,726 (20.07%)	21,941 (19.4%)	16,743 (19.1%)
III	12,766 (18.6%)	9,244 (18.8%)	9,078 (20.3%)	7,814 (20.2%)	21,844 (19.3%)	17,058 (19.4%)
IV	13,709 (20.0%)	9,938 (20.2%)	9,332 (20.9%)	8,110 (21.0%)	23,041 (20.3%)	18,048 (20.5%)
V—most deprived	14,735 (21.5%)	11,173 (22.7%)	9,290 (20.8%)	8,004 (20.7%)	24,025 (21.2%)	19,177 (21.8%)
Prior admission						
Malignancy	2,400 (4%)	1,682 (3%)	2,536 (6%)	1,755 (5%)	4,936 (4%)	3,437 (4%)
Cerebrovascular disease	2,023 (3%)	1,909 (4%)	2,084 (5%)	2,098 (5%)	4,107 (4%)	4,007 (5%)
Diabetes	709 (1%)	850 (2%)	619 (1%)	676 (2%)	1,328 (1%)	1,526 (2%)
Coronary heart disease*	4,484 (7%)	3,042 (6%)	3,165 (7%)	2,215 (6%)	7,649 (7%)	5,257 (6%)
Heart failure	2,747 (4%)	2,806 (6%)	5,895 (13%)	5,528 (14%)	8,642 (8%)	8,334 (10%)
Peripheral vascular disease	1,804 (3%)	1,060 (2%)	1,672 (4%)	886 (2%)	3,476 (3%)	1,946 (2%)
Respiratory disease	1,739 (3%)	1,298 (3%)	2,685 (6%)	2,017 (5%)	4,424 (4%)	3,315 (4%)

*Excluding myocardial infarction.
AMI = acute myocardial infarction.

the five years prior to their index admission with AMI (Table 1). Only 6% of this cohort had been admitted previously for CHD.

INDIVIDUALS WHO DID NOT SURVIVE TO REACH HOSPITAL. Compared to the hospitalized cohort, those who had a first AMI but did not survive to reach hospital were on average seven years older. However, the age difference between men and women was preserved. Again, there were proportionately more individuals from the most-deprived than from the least-deprived category. Thirty-three percent of individuals had at least one previous admission to hospital. Six percent had a prior admission with CHD.

Thirty-day case fatality. UNADJUSTED CASE FATALITY FOLLOWING HOSPITAL ADMISSION. Women had higher case-fatality rates at 30 days (27.2 vs 18.6%) and one year (38.0 vs. 26.7%) than men ($p < 0.0001$ for all comparisons). On this unadjusted basis, the greatest difference in case fatality occurred within 30 days (absolute difference 8.6%). Thereafter, women fared slightly worse, with an additional 10.8 versus 8.1% of men and women, respectively, dying within one year (Table 2).

ADJUSTED CASE FATALITY FOLLOWING HOSPITAL ADMISSION. When short-term case-fatality rates were analyzed according to gender and age group, younger women fared

Table 2. Unadjusted Case Fatality in Men and Women up to 30 Days Following a First AMI

	Proportion of All First AMIs Who Did Not Survive to Reach Hospital (%)		30-Day Case-Fatality Rate Following Admission to Hospital (%)		Overall 30-Day Case Fatality Rate Following First AMI (%)	
Age Group	Men	Women	Men	Women	Men	Women
<55 years	20.49	19.45	4.77	6.52	24.28	24.78
Numerator/denominator	3,788/18,490	931/4,786	701/14,702	251/3,855	4,489/18,490	1,182/4,786
55–64 years	30.17	28.29	11.31	13.48	38.08	38.13
	8,177/27,100	3,419/12,087	2,140/18,923	1,168/8,668	10,317/27,100	4,587/12,087
65–74 years	40.83	36.59	22.01	24.02	54.28	52.29
	15,228/37,297	9,640/26,344	4,857/22,069	4,012/16,704	20,085/37,297	13,652/26,344
75–84 years	55.04	50.06	35.41	35.91	70.64	68.86
	13,652/24,802	15,150/30,263	3,948/11,150	5,427/15,113	17,600/24,802	20,577/30,263
>84 years	68.13	66.68	46.06	45.04	81.93	81.32
	3,810/5,592	9,570/14,353	821/1,782	2,154/4,783	4,631/5,592	11,724/14,353
Overall	39.42	44.07	18.64	27.21	52.32	59.38
	44,655/113,281	38,710/87,833	12,792/68,626	13,366/49,123	57,447/113,281	52,076/87,833

AMI = acute myocardial infarction.

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Table 3. Adjusted Probability of Death in Men and Women up to 30 Days Following a First AMI

	Adjusted Male-to-Female Odds Ratio		
Age Group	30-Day Case Fatality in Those Admitted to Hospital	Death Before Reaching Hospital	30-Day Case Fatality in All AMIs
<55 years	1.25 (1.07–1.46)	0.86 (0.79–0.94)	0.94 (0.87–1.01) NS
55–64 years	1.16 (1.07–1.25)	0.86 (0.81–0.90)	0.93 (0.90–0.97)
65–74 years	1.08 (1.03–1.14)	0.82 (0.79–0.84)	0.89 (0.86–0.92)
75–84 years	1.00 (0.95–1.06) NS	0.83 (0.81–0.87)	0.87 (0.84–0.91)
>84 years	0.98 (0.88–1.10) NS	0.93 (0.9–0.99)	0.92 (0.85–1.0) NS

AMI = acute myocardial infarction; NS = nonsignificant.

worse than age-matched men, following a first admission for AMI (Table 3). For example, the approximately 4,000 women aged < 55 years had a 30-day case-fatality rate approximately 25% greater, in relative terms, than age-matched men. With increasing age, this disparity in 30-day survival was attenuated and even reversed in favor of women aged over 75 years (Fig. 1A). Overall, therefore, men and women >65 years had roughly equivalent case-fatality rates.

Inclusion of age into the logistic regression model accounted for most of the apparent effect of gender on case fatality at 30 days, with the unadjusted OR for case fatality in women declining from 1.63 (95% confidence interval [CI], 1.58 to 1.67) to an adjusted OR of 1.09 (95% CI, 1.06 to 1.13), though this residual difference remained significant ($p < 0.00001$). Adjusting for socioeconomic deprivation and comorbidity decreased the effect of gender still further.

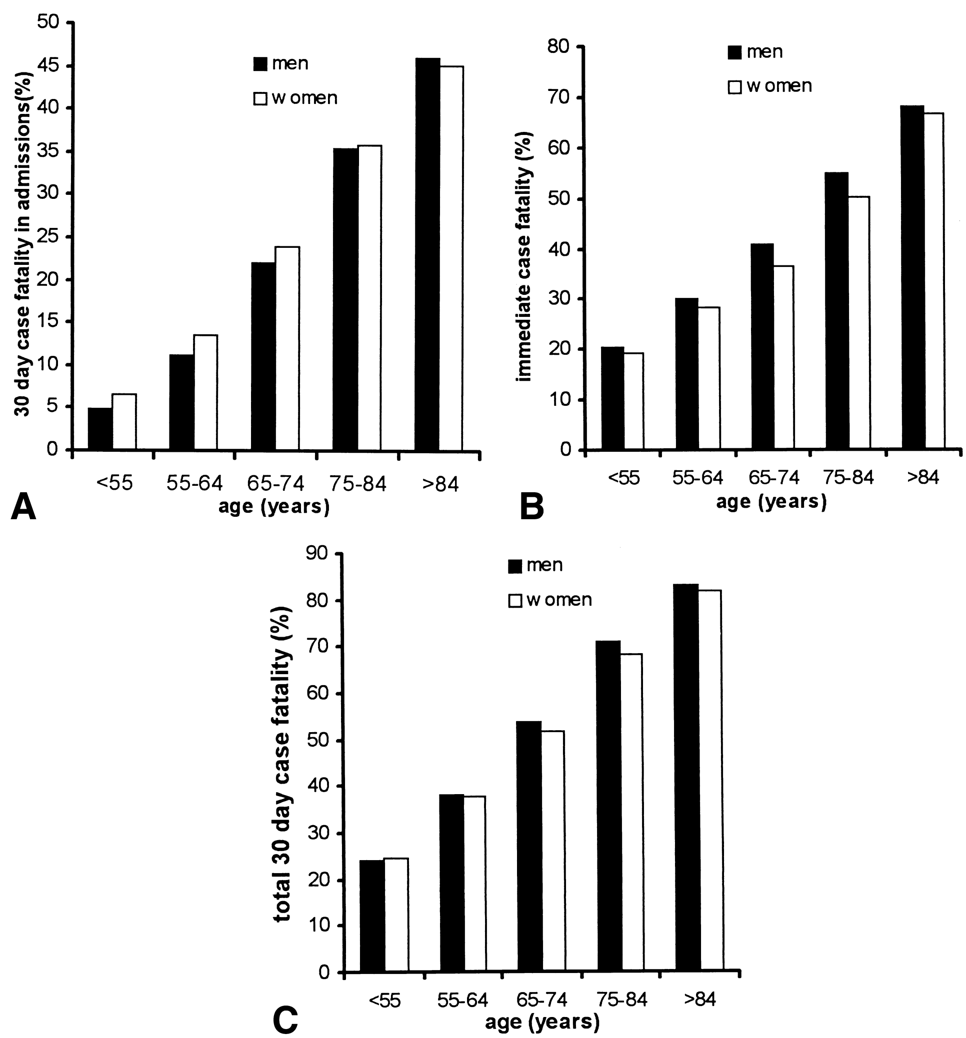

Figure 1. **(A)** Age and gender-specific 30-day case-fatality rates in patients admitted to hospital. **(B)** Immediate case fatality in all individuals with a first acute myocardial infarction. **(C)** Total 30-day case fatality including those individuals who did not survive to reach hospital.

An interaction term between age and gender added to the model was found to be highly significant ($p < 0.00001$). For every 10-year increase in age, the female-to-male OR decreased by 12%. There was, therefore, an increased risk of death in women at 30 days, which declined with increasing age, becoming nonsignificant by the age of 75 years. By the age of 80, men had a *relative* excess risk of 4%, which increased to 10% by the age of 85 (Fig. 1A).

Longer-term case fatality. ADJUSTED LONG-TERM CASE FATALITY FOLLOWING HOSPITAL ADMISSION. When case fatality was analyzed at one year in patients surviving beyond 30 days, adjustment of the logistic regression model for age accounted for all of the apparent effect of gender on case fatality, and the interaction between age and gender was nonsignificant ($p = 0.319$). In the longer-term, therefore, no difference was seen between men and women in case fatality in those individuals admitted to the hospital: OR = 0.97, CI 0.93 to 1.01 ($p = 0.1588$).

Individuals with a first AMI who did *not* survive to reach hospital. Figure 1B shows the age and gender-specific proportion of the total number of individuals who had a first AMI but who did survive to reach hospital. In contrast to the higher case-fatality rates seen among younger women *following* admission, men were more likely to die *before* hospitalization in each age group except the very elderly. Using multiple logistic regression to adjust for the effects of age, socioeconomic deprivation and comorbidity, gender was found to be a significant predictor of immediate death, following a first AMI ($p < 0.00001$). Again, a significant interaction existed between age and gender so that the effect of gender could not be simply described ($p = 0.0001$).

Overall (in-hospital and out-of-hospital) 30-day case fatality following first AMI. Analysis of 30-day case fatality in the *entire* cohort of first AMI and, therefore, incorporating and adjusting for "out-of-hospital" case fatality, was similar in men and women (Fig. 1C). Figure 2 shows the Kaplan-Meier survival curves for men and women age < 55 years (Fig. 2A) and 55 to 64 years (Fig. 2B). These age groups displayed the greatest discrepancy in 30-day case fatality between men and women following hospital admission. For example, in the under-55-year age group, 1% fewer women died before reaching the hospital (19.5 vs. 20.5%). However, in the first 10 days of hospitalization, women had a higher case fatality, so that by 30 days there were almost identical case-fatality rates for men and women (24.3 vs. 24.8%). Similarly, in those aged 55 to 64 years, 1.9% more men died before reaching hospital (30.2 vs. 28.3%), but at 30 days the case-fatality rates for men and women were similar (38.1 vs. 38.1%).

Analysis of the independent effect of gender on survival to 30 days in the entire cohort found gender to be a significant predictor of death, with women 9% more likely to survive to 30 days (CI 7% to 11%, $p < 0.0001$). Table 2 summarizes the relative contributions of death without hospitalization and death within hospital to the combined case-fatality rates at 30 days.

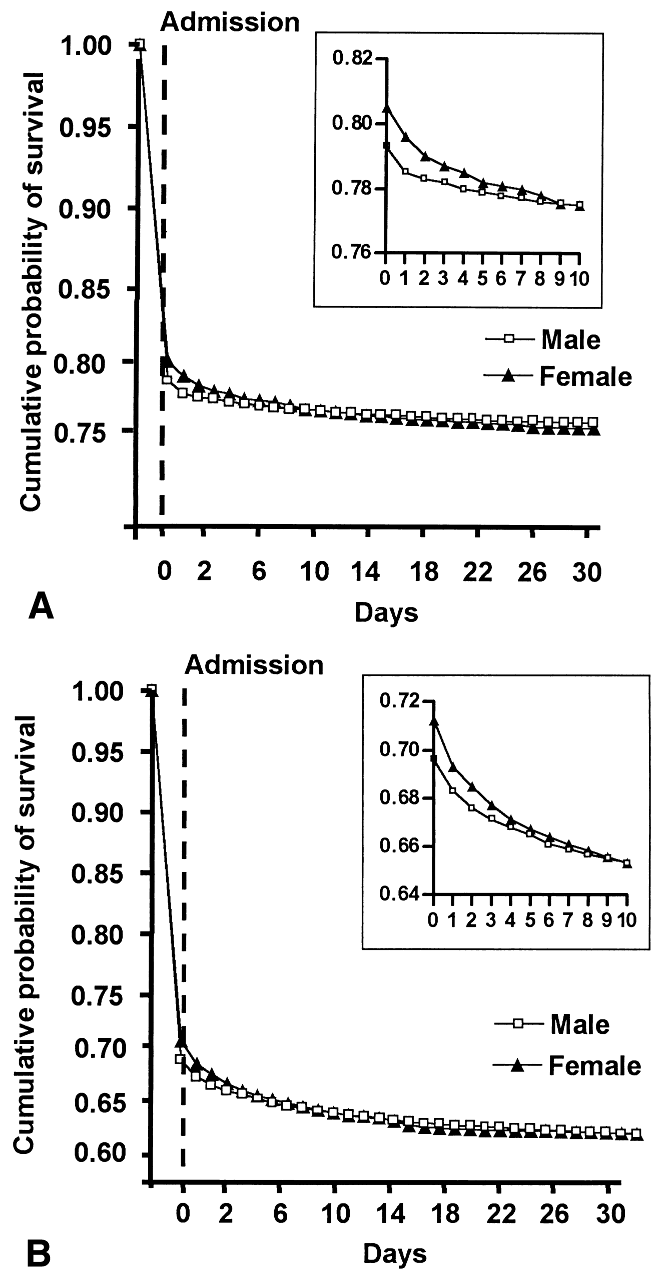

Figure 2. **(A)** Kaplan-Meier survival curve showing the cumulative probability of survival in all men and women aged <55 years with a first AMI. **(B)** Kaplan-Meier survival curve showing the cumulative probability of survival in all men and women aged 55 to 64 years with a first AMI.

DISCUSSION

This is the largest population-based study to examine both age and gender-based differences in short *and* long-term mortality following admission to hospital with a first AMI. Furthermore, this analysis incorporates data from individuals who do not survive to reach hospital.

Previous studies examining gender-based differences in survival following AMI. The existing literature presents conflicting evidence regarding the effect of gender on short-term case fatality following an AMI (5–7,9). A number of studies have shown that there is at most only a small independent association between gender and early case fatality after an AMI (7,17). However, these studies have usually failed to consider the varying effects of gender according to age, which may disguise differences and lead to inaccurate assessment of risk. A recent study by Vaccarino et al. (8) demonstrated that, after AMI, younger women, but not older women, had higher in-hospital case-fatality rates than age-matched men. Our analyses of AMI patients admitted to the hospital are consistent with Vaccarino et al. We demonstrated that the odds of death were 12% greater for women than for men for every 10-year decrease in age, whereas they showed a 7% excess risk for every five-year decrease.

Importance of age when considering the effect of gender on survival following AMI. We have found that gender-based differences in case fatality are present in the short term in patients admitted to hospital, confirming other reports (5,6). We have also found that the effect of gender in the short term varies with age and cannot therefore be simply described. That is, there was a significant interaction between age and gender. Young women fared worse than age-matched men, but in the elderly this pattern was reversed. However, once deaths following a first AMI in those patients who did not survive to reach hospital were taken into account, the interaction between age and gender became insignificant. Indeed, women were *less* likely to die at 30 days when these deaths were taken into account. The excess deaths occurring out of hospital in men offset the excess risk of death following admission to hospital in younger women. The interaction reported previously, therefore, *arose from* a selection bias introduced by neglecting those individuals who did not survive to reach hospital. In keeping with this, we have also shown that gender is not an independent predictor of longer-term case fatality. This finding, of course, should not detract from the need for aggressive treatment of younger women with AMI, especially as some reports suggest women are undertreated (18).

Possible mechanisms underlying the effect of gender on survival after AMI. Various mechanisms have been postulated to explain the apparent excess short-term risk in women following an AMI (8,19). These include gender-based differences in pathophysiology, including different plaque types, clotting mechanisms and coagulability. These are perhaps more likely to result in a persisting interaction between age and gender, which is not supported by our results. In our study, the effect of gender was no longer a significant predictor of outcome in younger age groups after 30 days. We have shown that younger men are more likely to die out-of-hospital before admission from their first AMI. Our findings are consistent with evidence that has shown that women are more likely to survive an out-of-hospital cardiac arrest (20). Though women survive more often to admission, they are more likely to die thereafter in hospital (21). Men are also more likely to have pre-existing coronary artery disease and lower left ventricular ejection fractions, which could explain why they are less likely to survive to reach hospital (21,22).

Study limitations. The apparent gender-based discrepancy in survival following admission to hospital was most evident in younger age groups. However, between ages 65 and 75 years there may be an overestimation of these deaths (23). Studies carried out in Finland, France and the United Kingdom suggest that death certification is generally accurate in these younger age groups (24,25). As recording of secondary diagnoses is poor, comorbidity in this study was based on the most reliable measure available, namely the principal diagnosis recorded in each previous admission. People with milder forms of the disease, which did not result in admission, would be missed. Therefore, this selection bias might overestimate the true impact of the comorbid conditions. A further limitation is that population-based data from hospital discharge at present lacks treatment and clinical detail. Finally, though some losses to follow-up might be expected, emigration of people of "pensionable age" from Scotland was <2% per decade.

Conclusions. We hypothesized that a higher proportion of men dying before they reach hospital might explain women's excess short-term case fatality. Our results support this hypothesis. We have shown that when deaths from AMI that occur without hospital admission are taken into consideration, the 30-day case-fatality rates are greater in men than in women. Thus, accounting for varying case-fatality rates before hospitalization seems to partly explain the gender-based differences observed in short-term case fatality in patients admitted to the hospital. Our finding that gender is no longer independently associated with longer-term case fatality in younger patients is consistent with other studies (26). Interactions between age and gender observed in short-term case fatality can be explained by variations in prehospital case fatality.

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